

Volatile anaesthetic myocardial protection: a review of the current literature

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ABSTRACT

Ischaemic preconditioning is a powerful innate adaptive phenomenon whereby brief periods of sublethal ischaemia result in marked tolerance to subsequent lethal ischaemia. Halogenated anaesthetics have been shown to mimic ischaemic preconditioning, modifying and attenuating ischaemia reperfusion injury.

This review aims to present the current animal and human data, discuss the possible mechanisms of action and review the clinical evidence for volatile anaesthetic-induced myocardial protection.

There is class Ia evidence for the myocardial protective properties of sevoflurane and desflurane in low risk patients undergoing coronary artery bypass grafting surgery.

These volatile anaesthetics have been shown to improve clinical outcomes and health economics following cardiac surgery, reducing intensive care and hospital stay. The evidence for the benefit of volatile anaesthetics in non-cardiac surgery is less robust and further large randomized controlled trials are required to elucidate this question.

Keywords: *volatile anaesthetics, myocardial protection, ischaemic preconditioning, mechanisms, cardiac anaesthesia, outcomes.*

INTRODUCTION

There is strong evidence for volatile anaesthetic induced myocardial protection in experimental studies.

Despite this weight of evidence in animal studies, the translational into human trials has borne less consistent results.

This review aims to present the current animal and human data, discuss the possible mechanisms of action and review the clinical evidence.

Mechanism of myocardial protection

Ischaemic preconditioning is a powerful innate adaptive phenomenon discovered by Murry and colleagues (1), whereby brief periods of sublethal ischaemia results in marked tolerance to subsequent lethal ischaemia. Halogenated anaesthetics have been shown to mimic ischaemic preconditioning, modifying and attenuating ischaemia reperfusion injury (2).

Two periods of ischaemic preconditioning have been described; early or classical preconditioning that occurs immediately, and induces potent protection that lasts one to two hours.

Late preconditioning or the second window of preconditioning occurs 24 hours after the initial stimulus, induces a less pro-

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nounced cardio-protection, but lasts for up to 72 hours (3).

Early and late preconditioning probably involves different signalling pathways that have yet to be fully elucidated. Early preconditioning is thought to involve opening mitochondrial ATP dependent potassium channels (4-9), increasing mitochondrial reactive oxygen species (4, 10, 11), decreasing cytosolic and mitochondrial calcium loading (12), protection of endothelial coronary cells by mediating nitric oxide release (13) and by suppressing neutrophil activation and the neutrophil-endothelium interactions that cause myocardial dysfunction (14, 15).

Pathways of late preconditioning involve attenuation of nuclear factor κ B (NF κ B), activation and reduced expression of tumour necrosis factor κ (TNF κ), interleukin 1 (IL1), intracellular adhesion molecules, eNOS, a reduction of the hypercontraction that follows reperfusion and activation of anti-apoptotic kinases (Akt, ERK 1-2) (2).

Volatile anaesthetics have been shown in a number of animal ex vivo and in vivo experiments to be able to precondition the myocardium in a similar way to classical ischaemic preconditioning. Similarly, volatile anaesthetics have the ability to post-condition the myocardium whereby exposure to volatiles during the reperfusion period also protects the myocardium (16). There is now increasing evidence that volatile anaesthetics can induce late preconditioning, raising the potential of myocardial protection that persists after the exposure in the operating theatre (16, 17).

In addition to the ability to precondition the myocardium, all volatile anaesthetics induce a dose dependent decrease in myocardial contractility, decrease myocardial oxygen demand and therefore improve myocardial oxygen balance during ischaemia. It is often difficult to experimental-

ly separate these two protective effects of volatile anaesthetics on the myocardium. This is best demonstrated by the fact that studies have also suggested the maximum protection is yielded by the administration of volatile anaesthetics throughout the operative procedure (18).

Clinical evidence in cardiac surgery

Since 1985, when Freedman and colleagues (19) reported that enflurane could improve post-ischemic myocardial recovery, there has been extensive research into the potential benefits of anaesthetic myocardial protection in both animal and human models. The majority have been performed on patients undergoing CABG (coronary artery bypass grafting). Unfortunately, to date, these studies have been observational in nature or if randomized have been too small and underpowered to identify effects on significant outcomes such as myocardial infarction and mortality. Studies have generally used surrogate markers for myocardial protection such as the cardiac troponins as a measure of myocardial injury.

To date there have been 3 meta-analyses performed including only randomized controlled trials (RCTs) to try and answer the question does volatile anaesthesia improve outcomes in coronary surgery?

Yu and Beattie performed the first meta-analysis in 2006 (20). The authors identified 32 randomized studies involving 2841 patients. Volatile anaesthetics included halothane, enflurane, isoflurane, sevoflurane and desflurane and were administered in any combination of the pre-bypass, during bypass and post-bypass periods. When compared with intravenous anaesthetics, those who were exposed to volatile anaesthetics had an observed reduction in mortality that did not reach statistical significance (OR, 0.65; 95% CI 0.36-1.18). Furthermore, removing studies that used halothane or enflurane in their study protocols also failed

to show a statistically significant reduction in mortality. Similarly, no statistical difference was seen in the incidence of AMI between groups. However, post hoc analysis of patients that received sevoflurane or desflurane showed that these patients experienced significantly less Troponin I leakage than patients receiving intravenous anaesthesia.

Symons and Myles performed a similar meta-analysis in 2006 (21). They identified 27 randomized studies including 2979 patients comparing volatile with non-volatile anaesthesia for CABG. Volatile anaesthetics again included halothane, enflurane, isoflurane, sevoflurane and desflurane and were administered during pre-bypass, bypass and post-bypass periods. There was no significant difference between volatile and non-volatile anaesthetic groups with respect to death, myocardial infarction, myocardial ischaemia or ICU length of stay. However, patients randomized to receive volatile anaesthetics had significantly higher cardiac indices, lower troponin I concentrations, reduced requirement for inotropic support, shorter duration of mechanical ventilation and shorter length of hospital stays than those randomized to receive intravenous anaesthetics. The results indicated that volatile anaesthetics may indeed be able to change outcomes in cardiac surgery.

More recent animal evidence suggests that sevoflurane and desflurane display more prominent cardioprotection than the older halogenated anaesthetics (22-26). This led to the most recent meta-analysis performed by Landoni and colleagues in 2007 (27). Their group identified 22 randomised studies involving 1922 patients where comparisons of the modern volatile anaesthetics sevoflurane and desflurane were made with intravenous anaesthesia in CABG surgery. Most studies were performed on patients undergoing on-pump CABG and most authors administered the volatile anaesthet-

ics throughout the entire procedure. Only a few of the RCTs were of high quality and all the studies included numbers that were too small to allow for assessment of important clinical outcome variables such as AMI and death.

Data pooling and analysis showed that when compared with intravenous anaesthesia, sevoflurane and desflurane were associated with significant reductions in the rates of all major clinical outcome variables. Volatile anaesthesia significantly reduced the degree of troponin I leakage (OR 0.47; 0.29, 0.76). Importantly, the risk of all-cause mortality and AMI was also significantly reduced by volatile anaesthesia (OR 0.31; 0.12, 0.80 and OR 0.51; 0.32, 0.84 respectively). Furthermore, the use of sevoflurane and desflurane was associated with a significant reduction in the duration of mechanical ventilation, length of ICU stay and time to hospital discharge.

Though this represents strong class Ia evidence for myocardial protection with modern volatile anaesthetic agents in patients undergoing CABG, results from a large observational study published in 2007 are not quite so conclusive. Data from a retrospective Danish database of 10,535 patients undergoing cardiac surgery with sevoflurane or propofol anaesthesia showed no difference in overall post-operative mortality or myocardial infarction (28). The group surmise that both propofol and sevoflurane have different cardioprotective properties. Sub-group analysis revealed that in patients undergoing non-coronary cardiac surgery, sevoflurane was superior to propofol whilst propofol was superior to sevoflurane in patients with severe ischaemia, cardiovascular instability or those requiring urgent surgery. This finding may reflect the antioxidant properties of propofol and the ischaemic preconditioning effect of unstable angina negating the myocardial protection offered by volatile anaesthesia.

Clinical evidence in non-cardiac surgery

Landoni and colleagues performed a meta-analysis of RCTs comparing sevoflurane or desflurane anaesthesia with intravenous anaesthesia in adult patients undergoing non-cardiac surgery in 2007 (29). Seventy-nine studies and over 6000 patients were included in the analysis but firm conclusions could not be made due to the low incidence of cardiovascular events in both groups.

Nevertheless, the most recent American College of Cardiology/American Heart Association Guidelines recommend the use of volatile anaesthetic agents during non-cardiac surgery in patients at risk for AMI (Class IIa, level B) (30).

CONCLUSIONS

There is class Ia evidence for the myocardial protective properties of sevoflurane and desflurane in low risk patients undergoing coronary artery bypass grafting surgery.

The modern volatile anaesthetics have been shown to improve clinical outcomes and health economics following cardiac surgery, reducing intensive care and hospital stay.

The evidence for the benefit of volatile anaesthetics in non-cardiac surgery is less robust and further large randomized controlled trials are required to elucidate this question. Furthermore, volatile anaesthetic protection of organs other than the heart warrants further investigation.

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